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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,421	09/16/2003	Ryan Bremer	039363-0703	3203

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,421	BREMER ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-18 and 120-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18 and 120-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/19/07 & 5/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

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5)☐ Claim(s) _____ is/are allowed.

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5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 18, 2007 has been entered.

The after-final amendment filed April 19, 2007 has been entered. Accordingly, claims 15, 120, 124, 129, and 134 have been amended, claim 19 has been canceled, and new claim 142 has been added.

Claims 15-18 and 120-142 are pending and under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 15-18 and 120-142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons of the rejections:

(a) The terms "with low, very low, or extremely low" in claims 15, 120, 124, 129, and 134 are relative terms, which render the claims indefinite. The term "with low, very low, or extremely low" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It should be noted that the terms with low, very low, or extremely low affinity are defined in the specification at page 58 as > 1 μM, 100 μM, and 1mM, respectively. See at page 58, paragraph 235. Thus, the three terms have overlapping scope, and one of ordinary skill in the art would not be able to differentiate between low, very low, and extremely low. For examination purposes only, the phrase is taken to mean that the compound has a KD > 1 μM.

(c) The phrases "binds weakly" in claim 128, and "weak binding compound" in claim 130 are relative terms, which render the claims indefinite. The terms "binds weakly" and "weak binding compounds" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without a standard, one of ordinary skill in the art would not be able to identify what binds weakly or the weak binding compound and those otherwise. For

examination purposes only, the phrase is taken to mean that the compound has a KD > 1 μM.

(d) PIM-1, PIM-2, and PIM-3 are protein kinases, which their amino acid sequences are part of the sequence listing. Thus, claim 18 and 120-142 are considered indefinite because it is not clear whether applicants refer to that of the sequence listing or some other proteins. Applicants should note that the claims are not in compliance with the sequence rules because the sequence is now listed in the sequence listing. Once a sequence is listed in the sequence listing a sequence identification number should accompany the protein/nucleic acid sequence at each occurance in the specification or the claims.

(d) Claims 16 and 17 are included in this rejection because they are dependent on rejected claims and do not cure their deficiencies.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 129-133, 139, and 140 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 129-133 and 139 are directed to methods of identifying ligands for PIM-1 that require the formation of cocrystals comprising any chemical compound bound to PIM-1 of any amino acid sequence, fragments, and mutants thereof. The specification, however, only provides the crystallization conditions for the catalytic domain of residues 29-313 of SEQ ID NO: 173 to obtain a crystal that is not described and a condition to obtain a co-crystal with undefined composition. Since the only structure described in the specification of a cocrystal is that of the well-known kinase inhibitor AMP-PNP, a nucleotide analog, bound to catalytic domain of residues 29-313 of SEQ ID NO: 173, the cocrystal obtain under this condition is that of said catalytic domain-AMP-PNP.

The court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] name chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly (43 USPQ2d 1398). For claims drawn to genus, MPEP section 2163 states

the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Also, MPEP section 2163 states that a representative number of species mean that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of invention, the full-length PIM-1 kinase and other related kinases, and their functions were well known in the art along with various classes of compounds that inhibits the actions of those enzymes. See for example U. S. patent 6,465,484. The instant claim are directed to a method of identifying inhibitors of PIM-1 kinase that requires obtaining of a cocrystal complex of any compound with any PIM-1 protein and its variants, homolog and fragments. It should be noted that: (a) compounds that are known to inhibit protein kinases by binding to the ATP binding site is of diverse structures, (b) protein kinases can be inhibited by compounds that binds to the protein binding site where an inhibitor specificity for the target enzyme can be engineered, and (c) another class of inhibitors of protein kinases are known as biligand inhibitors because they bind to both substrates binding sites. While the specification teaches the crystallization of, presumably, of a single example, of the inhibitors that bind to the nucleotide binding site, it fails to describe any additional species of those different classes of inhibitors described in (a), (b), and (c). Also, applicants should note that no crystal is described in the specification in any way. Thus, the specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the crystal containing the amino acid sequence of the catalytic domain of residues 29-313 of SEQ ID NO: 173 and crystallized under those conditions described in the specification in example 4, starting at page 100, for which no predictability of obtaining any crystal comprising any protein ligated with any chemical compound is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 129-133, 139, and 140 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to use the claimed method of the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to requirement of the method to obtain a cocrystal of any compound bound to any PIM-1 protein having any amino acid sequence, and variants and fragments thereof. Factors

to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed method requires the formation of a PIM-1 cocrystal having any chemical compound bound to any amino acid sequence, mutants and fragments thereof. The specification provides guidance and examples in the form of an assay to obtain a crystal of PIM-1 catalytic domain of residues 29-313 of SEQ ID NO: 173 and a cocrystal of, presumably, AMP-PNP bound to said catalytic domain of PIN-1 (see example 4). While molecular biological techniques and genetic manipulation to make any protein, a general crystallization methods for proteins, and synthetic method to make any compound that binds to PIM-1 are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of a particular protein and its complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form is highly unpredictable without any clear expectation of success, and any change in a given crystallization condition including any minor alteration could alter the crystal form and its diffraction characteristics or even lack of crystal formation. It is now evident that protein crystallization is the major hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of structure biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with protein crystals. See for example, Gilliland *et* al, (*Curr. Open in Struct. Biol.* 1996, 6, 595-603) in particular page 600, left column second paragraph; Ke *et al.* (Methods, 2004, 34, 408-414); and Wiencek, J. M. (Ann. Rev. Biomed. Eng. 1999, 1, 505-534). Thus, the skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallized. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Also, the formation of cocrystal is equally unpredictabl whether attempt to obtain the cocrystal by adding the ligand to an already formed crystal or by *de novo* co-crystallization of the protein in the presence of a ligand. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystal for a protein having the amino acid sequence of PIM-1 of SEQ ID NO: 173 or any crystal of any homolog, mutants, or fragment thereof suitable for structure determination by X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization

conditions or mutants or fragment of SEQ ID NO: 173 with or without any chemical compound which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the PIM-1 in the cocrystal, the chemical structure of a ligand which is binds to said PIM-1, and the crystallization conditions that produces a cocrystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Since the pending claims reads now on *in vitro* method of identifying ligands for PIM kinases, the rejections have been restated and modified to address the amendment to the previous claims.

Claims 15-19, 120-128, 134-138, 141, and 142 are rejected under 35 U.S.C. 103(a) as being unpatentable over 2004/0146942 ('942, IDS reference: A3, Weihe *et al.*) in view of the state of the art as exemplified by Dow *et al.* (J. Med. Chem. 1994, 37 2224-2231), U. S. patent 6,197,495 ('495), 6,465,484 ('484), and WO 01/87887 ('887).

The '942 document teaches a method of identifying inhibitors for the actions of PIM-1 kinase and PIM-3, kinase. See the abstract and paragraph 17, and claim 1. It teaches that compounds that bind to PIM-1 and PIM-3 have pain-regulating activity. See paragraphs 14-20. Also, it teaches assay methods of identifying the compounds that bind PIM-1 and PIM-3. See examples 2 and 3.

Dow *et al.* is relied on to demonstrate that there are reasons for one of ordinary skill in the art to select a compound with low affinity for a protein kinase over different compound with higher affinity for the target kinase. Specifically, they teach that through screening for compounds ellagic acid (compound 1) is a potent inhibitor of the tyrosine kinase pp60 with IC_{50} = 0.3 μM, and that it has poor selectivity profile for protein serine/threonine kinases. See the paragraph bridging the two columns at page 2224. On the bases of structural considerations, direct modification of compound 1 was not viewed as a viable option. Based on the molecular scaffold of compound 1, they identify the scaffold of compounds 5 and 9, which would provide for facile development of structure-activity relationships, in addition to probing binding interactions not readily

achievable through direct modification of compound 1. See the second paragraph, right column at page 2224. Both the unsubstituted compound 5a and 9a are competitive inhibitor of the kinase activity against the ATP substrate with lower affinity than compound 1 for the target kinase. See Tables 2-4.

The '495 patent is relied on to demonstrate the state of the art of identifying compounds that bind to the binding site of a protein using commercially available computer and software. See, in particular, columns 14-16.

The '484 teaches several derivatives of formula I of the instant application to be used as inhibitors of tyrosine protein kinase.

The '887 patent document teaches various derivatives of formula II of the instant applications. See, in particular, formula III at page 6. It teaches that the natural product K252a inhibits several classes of protein kinase. Also, it teaches that the X-ray structure of closely related natural product alkaloid, staurosporine, when bound to protein kinases CDK2 and cAPK confirmed that staurosporine acts as competitive inhibitor for the conserved binding site of adenosine triphosphate, which is found in all protein kinases and noted that a large number of natural products related to K252a structure (indocarbazoles) also inhibit various serine-threonine protein kinase. In addition, it teaches that most of these compounds have and desirable neuronal cytoxic effects due to their lack of specificity. See page 6, last paragraph.

The '942 document provides one of ordinary skill in the art with motivation to identify potential inhibitor for PIM-1 and PIM-3 as they teach that inhibitors of PIM-1 and PIM-3 regulate pain. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to develop a method of identifying potential inhibitors for PIM-1 and PIM-3. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to screen for compounds that bind to the target PIM-1, PIM-2, and PIM-3 to identify compound as a basic structure for further investigation. The selected compound for further investigation may not be the compound with highest affinity for the enzyme as many consideration are involved in selection of the compound to be derivatized such as the chemistry, metabolism, and toxicity of the compound (claims 15 and 124). See for example Dow *et al.* It should be noted that the ATP binding site is highly conserved among all protein kinases, and thus, a compound that binds to one protein kinase at the ATP site would be expected to bind to other kinases at some concentration (claim 16-18 and 125). Since the preferred compounds structures are those of formula I (benzimidazol), II, and III (quinoline) are purine analog and expected to inhibit the kinase activity through binding to the ATP binding site, residues 49, 52, 65, 67, 121, 128, and 186 are assumed to define the adenosine binding site. Thus any inhibitor that bind to the ATP binding site such a s those of formula I and II taught in the '484 and '887 patent are expected to interact with residues 49, 52, 65, 67, 121, 128, and 186 (claims 120-123, 134-138, 141, and 142). Thus, the claimed invention was within

the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

Claims 15-19, and 120-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mochizuki *et al.* (IDS reference: A187, J. Biol. Chem. 1999, 274, 18659-18666) in view of the state of the art as exemplified by Dow *et al.* (J. Med. Chem. 1994, 37 2224-2231), U. S. patent 6,197,495 ('495), 6,465,484 ('484), and WO 01/87887 ('887).

Mochizuki *et al.* teach that the *pim-1* oncogene encodes a serine/threonine kinase (PIM-1) involved in the transduction of cytokine-triggered mitogenic signal, and that PIM-1 is unique in that it is closely cooperates with c-Myc not only in oncogenisis, but also in apoptosis induction. See the abstract. They further teach that PIM-1 may contribute to transformation by inhibiting apoptosis. See page 18659, right column, the last third of the first paragraph.

The teaching of Dow *et al.*, '494, '484, and '887 are summarized above.

The '495 patent is relied on to demonstrate the state of the art of identifying compounds that bind to the binding site of a protein using commercially available computer and software. See, in particular, columns 14-16.

Mochizuki *et al.* provides one of ordinary skill in the art with motivation to identify potential inhibitor for PIM-1 as they teach PIM-1 contributes to transformation by inhibiting apoptosis. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to screen for compounds that bind to the target PIM-1, PIM-2, and PIM-3 to identify compound as a basic structure for further investigation. The selected compound for further investigation may not be the compound with highest affinity for the enzyme as many consideration are involved in selection of the compound to be derivatized such as the chemistry, metabolism, and toxicity of the compound (claims 15 and 124). See for example Dow *et al.* It should be noted that the ATP binding site is highly conserved among all protein kinases, and thus, a compound that binds to one protein kinase at the ATP site would be expected to bind to other kinases at some concentration (claim 16-18 and 125). Since the preferred compounds structures are those of formula I (benzimidazol), II, and III (quinoline) are purine analog and expected to inhibit the kinase activity through binding to the ATP binding site, residues 49, 52, 65, 67, 121, 128, and 186 are assumed to define the adenosine binding site. Thus any inhibitor that bind to the ATP binding site such a s those of formula I and II taught in the '484 and '887 patent are expected to interact with residues 49, 52, 65, 67, 121, 128, and 186 (claims 120-123, 134-138, 141, and 142). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nashed/
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Art Unit 1656